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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,199	10/15/2003	Paul Budworth	1392/11	6710

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EXAMINER	
JOIKE, MICHELE K	

ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
04/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/686,199	BUDWORTH ET AL.	
	Examiner	Art Unit	
	MICHELE K. JOIKE	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-10 and 12-19* is/are pending in the application.

4a) Of the above claim(s) *18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-10, 12-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 24, 2008 has been entered.

Amendments were made to claims 1, 5-9 and 13-16. Claims 4 and 11 are canceled. Claims 1-3, 5-10 and 12-19 are pending; claims 1-3, 5-10 and 12-17 are under consideration. Any rejection of record in the previous Office Action, mailed September 19, 2006 that is not addressed in this action has been withdrawn.

Response to Arguments Concerning Claim Rejections –35 USC §103(a)

Applicants' arguments filed on January 24, 2008 have been fully considered. The following grounds of traversal are presented:

Applicants argue that Cronan does not teach "binding partners" as meant by the Applicants, because the binding partners are provided, and there is no need to identify them. Applicants are using "binding partners" to mean molecules that bind to the protein of interest at areas other than the post-translational modification. Applicants also describe binding of both the affinity purification reagent and binding partners to the protein of interest. In Cronan, the binding partners relate to the affinity purification

reagent, rather than the binding partners in the claim. One of skill in the art would know that the phrase is being used differently in each case.

Applicants argue that there is no motivation to combine Fields with Cronan. First, there is no teaching or suggestion of identifying non-affinity purification reagent binding partners to the protein of interest in Cronan. Second, Fields teaches a yeast two-hybrid assay in which separation of the proteins of interest from the cell extract would make detection of the binding partner impossible, because the transcriptional activation reporter system requires the presence of the cellular extract to function. Every element of the claims cannot be present without destroying operability.

Applicants argue that there is no motivation to combine Cronan with Rigaut, and that Rigaut teaches away. Rigaut teaches away by expressly stating and demonstrating the necessity of having the two-step serial affinity purification procedure. One of ordinary skill in the art would not have had a reasonable expectation of success in combining Rigaut with the method in Cronan to obtain the single affinity reagent separation procedure.

Applicants argue that there is no motivation to combine Cronan with Luo. Luo is directed to the identification of protein-protein interactions within a cell. Separation of the proteins of interest from the cell extract would make detection of the binding partner impossible, because the transcriptional activation reporter system requires the presence of the cellular extract to function. Every element of the claims cannot be present without destroying operability.

Applicants' arguments have not been found persuasive for the following reasons.

In paragraph 23 of the specification, Applicants define binding partner. "[T]he term "binding partner" means any of a pair of organic chemical moieties which, under physiological conditions, associate non-covalently to form a complex. Examples of binding partners include, without limitation, receptors and ligands, antigens and antibodies, enzymes and substrates, biotin and streptavidin, carbohydrates and lectins, and the like." Cronan teaches that the binding partner can be an antibody, which the specification also teaches as a potential binding partner. Applicants argue that Applicants are using "binding partners" to mean molecules that bind to the protein of interest at areas other than the post-translational modification, however, that is not claimed. Applicants are also arguing that in Cronan, the binding partners relate to the affinity purification reagent, rather than the binding partners in the claim, however, that is not the case, since Cronan teaches that the binding partner can be an antibody.

Rigaut does not teach away. Rigaut does teach the use of a TAP tag, which is encoded by a fusion cassette of CBP, a TEV cleavage site and ProtA, for use in a two step procedure. However, Rigaut also mentions the use of CBP and ProtA by themselves (p. 1030), wherein ProtA showed 80% recovery of a fusion protein, and CBP showed 50% recovery of the fusion protein. Also Rigaut teaches that the second affinity step is performed to remove the TEV protease and to give a lower background. There is no indication to that the second affinity step is necessary to separate the complex from the extract and identify binding partners. Therefore, it does not teach away from a single affinity step. Furthermore, Cronan is the main reference and teaches the use of a singly tagged fusion protein and a single affinity step, and nothing

in Rigaut states that a single affinity step cannot be performed, in fact, it lists several identity tags that can be used in single affinity steps.

Applicants argue that combining Luo with Cronan or Fields with Cronan destroys operability because separation of the proteins of interest from the cell extract would make detection of the binding partner impossible, because the transcriptional activation reporter system requires the presence of the cellular extract to function. Luo is not being used as a reference to teach the performance of a yeast two-hybrid. Luo is being used to teach that identifying protein interactions in mammalian cells is desirable because post-translational modification is different in mammals than in other organisms, for example, yeast. Therefore, combined with Cronan and Rigaut these references teach a method for obtaining *in vivo* binding partners of a protein of interest. However, Cronan also teaches use of a mammalian cell (column 12), so the Luo reference has been removed.

Applicants' traversal is found to be persuasive in that Fields does teach the identification of binding partners in the presence of the cellular extract. However, applicants' amendment has necessitated the new grounds of rejection under 35 U.S.C. 103(a) recited below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-10 and 12-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronan in view of Rigaut et al.

Applicants claim a method for obtaining *in vivo* binding partners of a protein comprising obtaining a cell and expressing a fusion protein comprising a protein of interest and a post-translational modification sequence; growing the cell under conditions to permit expression and modification; contacting the cell extract with an affinity purification reagent; and separating the complex from the extract. The fusion protein is a heterologous protein, and there is a cleavage site between the protein of interest and the post-translational sequence. The method also includes identifying binding partners, including a plurality of binding partners. The method can also be performed by transforming a cell with a vector encoding the fusion protein. The fusion protein comprises an affinity purification sequence, wherein the purification sequence is a *S. aureus* protein A IgG binding domain or a calmodulin binding peptide and affinity purifying the protein of interest after the separating step.

Cronan (U.S. 5,252,466, specifically Summary of Invention, 1st, 4th and 5th paragraphs, Field of Invention, Detailed Description, p. 13 and 18, Examples 1 and 7, Claims 1, 2 and 7) teaches a method for obtaining *in vivo* binding partners of a protein comprising obtaining a transformed host cell (bacteria, yeast, other fungi, plant, insect or mammalian) and expressing a fusion protein comprising a protein of interest and a post-translation biotination sequence (Applicants teach that biotin can be a tag on page 3 of their specification); growing the cell under conditions to permit expression and

modification; contacting the cell extract with an affinity purification reagent; and separating complex from the extract. The fusion protein is a heterologous protein, and there is a cleavage site between the protein of interest and the post-translation biotination sequence. The method can also be performed by transforming a cell with a vector encoding the fusion protein. However, Cronan does not teach identifying any binding partners that bind said protein of interest in said complex, or cleaving the protein of interest from the post-translational modification sequence prior to identifying binding partners of the protein of interest.

Rigaut et al (Nature Biotech, 17: 1030-1032, 1999, see entire article) teach a transformed yeast cell with a fusion protein comprising a heterologous protein with two affinity tags, a *S. aureus* protein A IgG binding domain and a calmodulin binding peptide, as well as a TEV cleavage site. They also teach use of a single affinity tag, either use of CBP or Prot A, for example. They teach making a cell extract and purification of the protein of interest, and identifying proteins that bind the protein of interest by mass spectrometry. They also teach that the target protein is cleaved before purification and electrophoresis. Therefore, the target protein is cleaved from the post-translational modification sequence prior to identifying binding partners of the target protein.

The ordinary skilled artisan, desiring to perform a method for obtaining *in vivo* binding partners of a protein comprising obtaining a cell and expressing a fusion protein comprising a protein of interest and a post-translational modification sequence; growing the cell under conditions to permit expression and modification; contacting the cell

extract with an affinity purification reagent; separating complex from the extract with; and identifying any binding partners, with the fusion protein being a heterologous protein, and a cleavage site between the protein of interest and the post-translational sequence, and to use a fusion protein comprising an affinity purification sequence, wherein the purification sequence is a *S. aureus* protein A IgG binding domain or a calmodulin binding peptide and affinity purifying the protein of interest after the separating step, would have been motivated to combine the teachings of Cronan of obtaining a cell and expressing a fusion protein comprising a protein of interest and a post-translational modification sequence; growing the cell under conditions to permit expression and modification; contacting the cell extract with an affinity purification reagent; and separating complex from the extract with the teachings of Rigaut et al, of a fusion protein comprising an affinity purification sequence, wherein the purification sequence is a *S. aureus* protein A IgG binding domain or a calmodulin binding peptide, affinity purifying the protein of interest after the separating step, and identifying binding partners. There would be motivation to combine the teachings because affinity tagging allows for rapid purification of proteins, especially heteromeric complexes, including proteins interacting with other proteins. Rigaut et al teach that calmodulin binding peptide allows for efficient selection and specific release from the affinity column under mild conditions, and that ProtA allows fro efficient recovery (80%) of a fusion protein present at low concentration in a complex mixture. It would have been obvious to one of ordinary skill in the art to use affinity tagging for purification because these affinity tags do not impair function and allow for efficient recovery. Given the teachings of the

prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELE K. JOIKE whose telephone number is (571)272-5915. The examiner can normally be reached on M-F, 9:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michele K Joike, Ph.D./

Michele K Joike, Ph.D.
Examiner
Art Unit 1636